REMARKS

Claims 1-26 are pending in the application. Claims 6-20 are withdrawn from consideration. Claims 1-5 and 21-26 are rejected. Applicants previous amendment filed August 25, 2003 has not been entered.

Claims 1-5 and 21-26 cancelled. New claims 27 and 28 are added. In view of the above amendments and the remarks below, the applicants request consideration of claims 27 and 28.

Rejections under 35 U.S.C. § 112

Claim 23 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. In the interest of furthering prosecution of the application, applicants have cancelled claim 23, and suggest that the rejection of that claim under 35 U.S.C. § 112 is therefore moot.

Rejections under 35 U.S.C. § 102

Claim 5 is rejected under 35 U.S.C. § 102(a) as being anticipated by Accession number AF136379 (June 2000). Claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by Accession number Z78129 (August 1997). Claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by Accession number U55870 (May 1996). The action indicates that the cited references disclose sequences that include the indicated SEQ ID Nos. of claim 5, and therefore meet the limitation of "a nucleotide comprising a conserved portion in the nucleic acids of enteroviruses" as the recitation of 'comprising' encompasses sequences on either side of the conserved portions.

Applicants have cancelled claim 5 and added new claims 27 and 28 which are drawn to

selected kits useful for the detection and differentiation of enterovirus in a sample. New claims 27 and 28 utilize "consisting of" language rather than "comprising" language. Applicants suggest that the cited references fail to disclose the discrete conserved portions of the enterovirus nucleotide sequences set out in new claims 27 and 28. In view of the above amendment, the applicants suggest that the rejection of claim 5 is rendered moot, and that claims 27 and 28 are not anticipated by the cited references.

Rejections under 35 U.S.C. § 103

Claims 1-5 and 21-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kilpatrick (U.S. Patent No. 6,168,917) in view of Accession numbers U22521 (January 1997), AF 177911 (September 1999), AF136379 (June 2000), U55870 (May 1996) and Z78129 (August 1997) and further in view of Accession number E30248 (from JP 1999346799).

Applicants have cancelled claims 1-5 and 21-26 and added new claims 27 and 28 which are drawn to selected kits useful for the detection and differentiation of enterovirus in a sample. The kit of claim 27 includes at least a pair of oliognucleotide primers for nucleic acid amplification, and at least one synthetic nucleotide sequence fixed on a solid substrate. The kit of claim 28 includes at least one synthetic nucleotide sequence fixed on a solid substrate. New claims 27 and 28 utilize "consisting of" language rather than "comprising" language, and Applicants suggest that the cited references fail to suggest that the discrete conserved portions of the enterovirus nucleotide sequences set out in claims 27 and 28, fail to suggest the utility of such conserved regions for simultaneous detection and differentiation of enterovirus, and fail to suggest the advantageous sensitivity of a kit including a nucleotide sequence selected from SEQ ID Nos 9-15 fixed on a solid substrate, as set out in claims 27 and 28.

The action indicates that an ordinary artisan *would have been able to* develop primer pairs and nucleotide sequences that would specifically detect Enterovirus 72 and Coxsackievirus A16, and that "given that the sequences of the genome of many enteroviruses were already sequenced and readily available, *it would have been well within the skill of the ordinary artisan* to align these known sequences and identify conserved and variable regions" (emphasis added). However, as set out at MPEP § 2143.01, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination, and the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish prima facie obviousness, without some objective motivation to combine the teachings of the references.

In addition, "obvious to try" is not the standard for establishing *prima facie* obviousness under 35 U.S.C. § 103, rather a reasonable expectation of success of the claimed invention is required, and that reasonable expectation must be found in the cited references themselves (see MPEP 2143.02).

Applicants suggest that the cited references fail to provide motivation to modify the references so as to arrive at kits of claims 27 and 28, and that the cited references fail to provide a reasonable expectation of success of those kits. Applicants therefore suggest that the cited references, singly or in combination, fail to establish the *prima facie* obviousness of newly added claims 27 and 28 under 35 U.S.C. § 103.

However, even if *prima facie* obviousness were established, applicants suggest the *prima facie* case can be rebutted by a showing of the unexpected and advantageous properties

of kits, as acknowledged in a peer-reviewed scientific journal.

Applicants hereby provide a copy of the journal article Shih et al. (*Journal of Virological Methods* 111, 55-60 (2003)) that supports the advantageous sensitivity that may be achieved using the kits of claims 27 and 28. The Shih et al. reference is related to the serotype-specific detection of enterovirus RNA using a DNA microchip array according to an embodiment of the currently claimed kits in the invention. Two of the instant inventors are coauthors of the paper.

The methods and materials described in the published paper are largely the same as those described in the present application, including the design of the primers and the probes used (see Shih et al. at page 56 "Materials and Methods", in particular section 2.2 RNA isolation, cDNA synthesis, and PCR amplification. As shown by Shih et al., the detection capability of a microchip is more sensitive than that of a PCR reaction:

> "To determine how many viruses must be present in a specimen before they can be detected by the EV71 microchip, a series of various dilutions of viruses (strain BrCr) were added to a negative specimen. The virus titer was measured by plaque assay. Meanwhile, RT-PCR was performed with RNA samples isolated from each of the serial dilutions. The amount of template RNA corresponding to 10^2-10^3 virions was needed to produce a visible specific amplicon on the agarose gel (data not shown). However, the EV71-microchip can detect the amplicon derived from viral RNA corresponding to 1-10 virions" (Shih et al. p. 58, col. 2, first full paragraph).

Although the Kilpatrick reference describes the detection of viral RNA in a sample, "PCR with degenerate primers has been shown to detect as little as 100 fg [femtograms] of poliovirus RNA" at col. 20, lines 4-13). In contrast, using the kits of claim 27 and 28, as

described by Shih et al. results in the ability to detect 1-10 virions of the target virus (as discussed above). In order to show the substantially increased sensitivity of the Shih et al. assay, we should convert the virions to a weight of RNA detected.

Even at a sensitivity of 10 virions (the upper limit provided by Shih et al.), the assay is able to detect 10 copies of the enterovirus genome. The genome of an enterovirus includes approximately 7,500 nucleotides, and the average molecular weight of a single nucleotide is approximately 330 grams/mole. There are Avogadro's number, or 6.022×10^{23} particles in a mole. Therefore, the weight of RNA corresponding to 10 virions may be approximated as follows:

$$10 \text{ virions} = \frac{(10 \text{ genome copies}) \times (7{,}500 \text{ nucleotides/copy}) \times (330 \text{ grams/mol nucleotides})}{(6.022 \times 10^{23} \text{ nucleotides/mol nucleotides})}$$

$$10 \text{ virions} = 4.11 \times 10^{-17} \text{ grams} = 0.04 \text{ femtograms}$$

That is, the assay of Shih et al. is approximately 2,400 - 24,000 times more sensitive than the assay of Kilpratick. Put another way, for a practitioner to utilize the methods of Kilpatrick to detect enteroviruses in a sample, the templates in the sample must reach ~2,400 copy numbers of the enterovirus genome in order to be detected. As the currently claimed kits permit detection of 1-10 virions (or copies of the genome) they offer dramatically enhanced sensitivity.

The sensitivity of detection made possible using the kits of claims 27 and 28 would not be considered obvious by one of ordinary skill in the art in view of the cited references.

Although the Kilpatrick reference teaches a method to detect minority populations of enteroviruses in mixed serotype cultures, the Kilpatrick reference neither teaches nor suggests the unexpected sensitivity of the presently claimed kits. Accordingly, applicants suggest that a rejection of claims 27 and 28 under 35 U.S.C. § 103 would inappropriate.

The above amendments and remarks are believed to address fully the Examiner's rejections, and place the application in condition for allowance. A prompt indication of the same respectfully is requested. The Examiner is encouraged to telephone the undersigned if any issues remain that may be resolved by a telephonic interview.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on November 19, 2003.

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